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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/712,481	11/13/2000	Kyoichi Watanabe	SCH2000	9803
20786	7590	05/24/2004	EXAMINER	
KING & SPALDING LLP 191 PEACHTREE STREET, N.E. ATLANTA, GA 30303-1763			CRANE, LAWRENCE E	
			ART UNIT	PAPER NUMBER
			1623	

DATE MAILED: 05/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/712,481	<b>Applicant(s)</b> WATANABE ET AL.	
	<b>Examiner</b> L. E. Crane	<b>Art Unit</b> 1623	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02/03/2004 (Resp. Restr. Req.).
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,44,47 and 56-67 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,44,47 and 56-67 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

Claims **3-43, 45-46 and 48-55** have been cancelled, claims **1, 44 and 47** have been amended, and new claims **56-67** have been added as per the amendment filed February 3, 2004. The supplemental submission of a corrected declaration is also noted. No additional Information Disclosure Statements (IDSs) have been received as of the mailing date of this Office action.

Claims **1-2, 44, 47 and 56-67** remain in the case.

Applicant's election without traverse of Group **I** in Paper No. 02032004 is acknowledged.

Applicant's election of Group **I**, claims **1-2** and linking claims **44 and 47** to the degree applicable in Paper No. 02032004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP §818.03(a)).

The disclosure is objected to because of the following informalities:

On page 9 at line 6, and on page 46 at line 9, the second ring containing chemical formula is technically incorrect. The heterocyclic ring should be amended to represent -- 3-pyrrolyl --.

On page 93, line 12, the term "thiophosogene" is a misspelling of -- thiophosgene --.

Appropriate correction is required.

Incorporation by reference of essential material by reference to a foreign application or a foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by applicant, or a practitioner representing applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCAP 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In each of the above cases, the incorporations are of the complete document, and fails to properly point out the particular portions of the US patent(s) being incorporated; see MPEP §608.01(p)(1)(A) noting *In re de Seversky* and in the same paragraph (column 2 of p. 600-769, August 2001 edition) the instruction which reads as follows: “[p]articular attention should be directed to specific portions of the referenced document wherein the subject matter being incorporated may be found.”

In addition, each of the above incorporations represents a failure to provide specific disclosure of how to make and/or use. Therefore, the above citations of the *Hawkins* decisions continue to apply to all incorporations by reference.

The attempt to incorporate subject matter into this application by reference to US patent **4,522,811** at page 39, line 2, is improper because the particular portions of the noted patent have not been incorporated as provided for by *Hawkins*.

Claims **1-2, 44, 47 and 56-67** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; the scope is excessive in view of the disclosed exemplifications.

In claim **1** at line 8, the term “O-S(=O)<sub>n</sub>-R<sup>5</sup> or O-C(=O)-R<sup>5</sup>” is directed to two substituents wherein the replacements of same by hydrogen are not disclosed within the examples and are therefore not properly enabled for the instant claims. In addition in claim **1** at line 6 and in claim **59** at line 3 the pyrrole containing substituent has not been enabled in any exemplification within the instant disclosure. Therefore, the scope of the claims exceeds the enabled scope of the disclosure as regards the noted substituents.

Claims **1-2, 44, 47 and 56-67** is/are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8

USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims includes embodiments at the 2'-O- location which have not been enabled by examples in the disclosure as noted in the above scope rejection.

B. The nature of the invention is directed to a process of making 2'-deoxy-L-ribonucleotides by initial formation of a 2'-thiocarbonyl derivative followed by contact with tributyl-tin-hydride, presumably in the presence of a free radical initiator, e.g AIBN or an equivalent.

C. The state of the prior art is well developed as demonstrated by the substantial quantity of prior art provided by applicant and by examiner as noted on the PTO-1449 and PTO-892 forms.

D. The level of one or ordinary skill is high because the process being claimed is very well known in the art as demonstrated by the **Barton et al.** reference cited in the art rejection below.

E. The level of predictability in the art is high because the reaction originally developed by Barton et al. is well developed for a large number of compounds from nucleosides to steroids.

F. The amount of direction provided by the inventor is limited in the "Examples" section to 2'-O-phenoxythiocarbonyl and 2'-O-imidazolothiocarbonyl.

G. The existence of working examples is limited to thiocarbonyl derivatives already well known in the art.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be undue because three of the newly proposed substitutes for phenoxythiocarbonyl are not known in the prior art, and because applicant has not provided any exemplifications to support the suggestion that these substitutions are possible in actual practice.

Claim 66 is objected to because of the following informalities:

In claim **66** at line 6, the term “C<sup>5</sup>-nitorpyrimidine” is apparently a misspelling of -- C<sup>5</sup>-nitropyrimidine --.

Appropriate correction is required.

Claims **1-2, 44, 47 and 56-67** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims **1, 44 and 58-65** provide for the use of a reagent capable of “selectively activating” the 2’-hydroxyl of a  $\beta$ -L-nucleoside, but, since the claims do not set forth any step(s) involved in the method/process, it is unclear what method/process applicant is intending to encompass; e.g. what reagent(s) and protecting groups are required to effect the claimed “selective activation.” A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. The same criticism applies to step “b)” in claim **1** wherein the terms “reducing” and “a reducing agent” fail to adequately define the process step (reagent(s) and protecting groups) being claimed. See also claim **44** at line 18 wherein the reagent(s) and protecting groups required to effect “condensing” of the particular heterocyclic and carbohydrate compounds have not been specified. See also claim **47** wherein the reagent(s) and protecting groups required to effect “epimerizing” of the 3’-OH group have not been specified. This rejection applies to all claims (**1, 44, 47, etc.**) wherein the noted terms are used generically to suggest a process step without providing sufficient details defining the reagents and protecting groups required to execute the claimed process. Examiner notes in particular that tributyl-tin-hydride (specified as “the reducing agent” in claim **2**) is not known to be effective as a reducing agent in the absence of a free radical initiator (see PTO-892 ref. S), a limitation which applicant has failed to include within the instant claims, and which limitation is clearly present in the examples; e.g. see Example 12 at page 77, etc.

In claim **1**, lines 5 and 8, the terms “the following:” and “or” render the claim equivocal because the lists of substituent group alternatives being advanced are not clearly presented. Markush groups are properly formulated with the term -- selected from the group consisting of [A], [B], ... **and** [R] --; see MPEP at §2173.05(h)(I). Alternatively, the MPEP at §2173.05(h)(II) provides for the listing of alternative substituent groups with “or” between the last two items. Applicant is respectfully requested to pick one alternative or at least to not mix formats. For similar errors see also claim **44** (lines 12 and 15).

In claim 44 at line 15, the term “not limited to” is open ended terminology which admits that the claim is indefinite because all of the alternative substituent groups have not been defined in the claim.

In claims 64-67 the terms or prefixes “alkyl,” “vinyl,” “acetylenic,” “acyl,” “amido,” “hydroxyalkyl,” and “thioalkyl” are either incomplete or lack an upper bound because the noted terms have not been defined in the claim as having size limits (indefinite metes and bounds) and/or have not further specified the location, specific type, and/or orientation of the group in the claims; e.g. “amido” is generic for carboxamido, sulfonamido, phosphoramido, etc. and does not provide any indication of the orientation of the group.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

“A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.”

Claims 1-2, 44, 47 and 56-67 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Barton et al.** (PTO-892 ref. S) in view of **Boudou et al.** (PTO-1449 ref. BA).

The instant claims are directed to a process of making 2'-deoxy-L-ribonucleotides by initial formation of a 2'-thiocarbonyl derivative followed by contact with tributyl-tin-hydride, presumably in the presence of a free radical initiator, e.g AIBN or an equivalent.

**Barton et al.** discloses in Scheme 1 at page 152 the generic process of converting a hydroxyl group to hydrogen via thiocarbonylated intermediates which are then subjected to free radical reduction in the presence of tributyl-tin-hydride and a free radical initiator. In Scheme 2 at page 153 Barton further specifically discloses that two of the thiocarbonyl derivatives (first and third structures at lines 6-7 of claim 1) are known to be effective intermediates and in light of the Hass-Henze doctrine examiner presumes in the absence of evidence to the contrary that the ethyl xanthate analogue is an obvious variant (see Barton at page 156, part “D,” second paragraph, which teaches that all of the reagents are fast with methyl xanthate noted to be the most quickly reduced derivative). And lastly at pages 166-167, Barton discloses that adenosine may be converted to 2'-deoxyadenosine via a 3',5'-protected

intermediate wherein the 2'-O-phenoxythiocarbonyl group is replaced by hydrogen by the actions of tributyl tin hydride and AIBN.

**Barton et al.** does not expressly disclose that an L-ribonucleoside has been converted to its 2'-deoxy analogue.

**Boudou et al.** discloses at page 608, Scheme 2, step ii, that <sup>L-</sup>adenosine protected at its 3' and 5'-hydroxyl locations is transformed via a 2'-O-phenoxythiocarbonyl derivative into its 2'-deoxy analogue following contact with tributyl tin hydride and AIBN.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made after review of the above prior art to substitute various different thiocarbonyl derivatives taught by Barton et al. in the course of routine experimentation to optimize the noted prior art process of the Boudou reference .

One having ordinary skill in the art would have been motivated to combine these references because both references deal in part with the conversion of carbohydrate moieties into deoxy analogues thereof using metal hydride/free radical initiator induced reduction of the thiocarbonyl derivative of the hydroxyl to be replaced by hydrogen.

Therefore, the instant claimed process of making 2'-deoxynucleosides from their ribonucleoside analogues via partially protected would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX



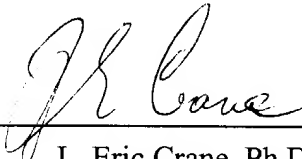
(unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec  
05/19/2004



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L. Eric Crane, Ph.D. Esq.  
Patent Examiner  
Technology Center 1600